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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/249,543	02/12/1999	THOMAS C. EVANS	NEB-154	1052

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/249,543	EVANS ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16-27, 29 and 30* is/are allowed.

6)☒ Claim(s) *1, 2, 7-9, 14, 15, 24 and 28* is/are rejected.

7)☒ Claim(s) *3-6 and 10-13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Inventorship

In view of the papers filed February 1, 2002, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding co-inventor Shaorong Chong. The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Response to Amendment

Applicant's Amendment B, Paper No. 9 filed February 1, 2002, has been entered and the amendments to claim 2, 8, 16, 17, 28, and 29 overcome the rejection of record of claims 2, 8, 16, 17, 28, and 29 under the second paragraph of 35 U.S.C. §112. Applicant's arguments at pages 5 and 6 of Paper No. 9, responsive to the enablement rejection of record of claims 1-4, 6, 8-12, 15-19, 21, 24, 25, 27 and 28 under the first paragraph of 35 U.S.C. §112 are persuasive and the rejection is withdrawn as Applicant's arguments are supported by the teachings of Canne et al., Hondal et al., and Nilsson et al., cited by Applicant, as well as by the U.S. Patents to Canne et al. and Tam, cited below and made of record herewith. These disclosures establish that the methods claimed herein may utilize another amino acid, e.g., selenocysteine, available through eukaryotic ribosomal translation, in addition to cysteine at the amino-terminus of a second target protein.

Rejections of record of claims 1 and 15 over publications of Evans et al. and Severinov under 35 U.S.C. §102(a) are withdrawn in view of the Declaration under 37 CFR 1.131 of Dr. Thomas C. Evans filed with Paper No. 9 February 1, 2002, and the documentary evidence attached thereto, which Declaration avows, and which evidence demonstrates, a

reduction to practice of the claimed invention prior to the June 1998 publication dates of Evans et al. and Severinov et al. The rejection of record of claims 24 and 28 under 35 U.S.C. §102(a) however cannot be overcome solely on the basis of the Petition to amend inventorship under 37 CFR 1.48(a) filed February 1, 2002, granted above. It will be necessary to demonstrate that the article by Chong et al. is unavailable as prior art to an invention of theses claims by, e.g., a Declaration under 37 CFR 1.132 by Dr. Shaorong Chong, avowing that the co-authors of Chong et al. were not co-inventors of subject matters of claims 24 and 28. Because new grounds of rejection over the prior art are stated herein, this communication is not made final.

Claim Rejections - 35 USC §§102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. §102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. §122(b). Therefore, this application is examined under 35 U.S.C. §102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. §102(e)).

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37

CFR §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Claims 24 and 28 are for reasons of record rejected under 35 U.S.C. §102(a) as being anticipated by Chong et al., 1998, **The Journal of Biological Chemistry**, Vol. 273, pages 10567-10577.

Chong et al. disclose, see pages 10572-10573 and accompanying Table IV and Figs. 4 and 5, the preparation of a modified intein comprising a mutant intein, having the amino acid substitution H453Q and capable of pH and temperature-induced *in vitro* cleavage between the intein C-terminus and the adjacent extein N-terminus producing a specified residue, alanine, at that N-terminus. Chong et al. also disclose, page 10568, preparation of a plasmid, pMYT4, wherein a DNA sequence encodes the modified, mutant, intein.

Claims 1 and 15 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Canne et al., U.S. Patent No. 6,326,468.

Available as prior art under 35 U.S.C. §102(e) in view of their provisional filing date, Canne et al. disclose, see cols. 14-15, the preparation of a protein wherein the process of intramolecular acyl transfer is used to ligate a first target protein generated with a C-terminal thioester to a second target protein generated with a specified amino terminal amino acid, a cysteine, to form a fusion polypeptide. Claim 1 does not require the **recombinant** expression of either a first or a second target protein, thus the design and preparation of the first and second target proteins of Canne et al. are considered to be expressions of proteins for purposes of this rejection, anticipating the claimed subject matter. In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method disclosed by Canne et al. with a **recombinantly-expressed** second target protein because Canne et al. teach, col. 5, lines 27-31, that such a protein ligated by the method may be "recombinantly expressed".

Claim 1 and 15 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Tam, U.S. Patent No. 6,310,180.

Tam discloses, see Figure 26 and discussion at cols. 36-42, a method for the fusion of proteins wherein the process of intramolecular acyl transfer is used to ligate a first target protein generated with a C-terminal thioester to a second target protein generated with a specified amino terminal amino acid, a cysteine, to form a fusion polypeptide. Claim 1 does not require **recombinant** expression of either a first or a second target protein, thus the design and preparation of the first and second target proteins of Tam are considered to be expressions of proteins for purposes of this rejection, anticipating the claimed subject matter. In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method disclosed by Tam with both a **recombinantly-expressed** first and second target protein because Tam teaches, col. 41, lines 54-57, that proteins to be ligated by the method include those available from, and "derived from . . . recombinant DNA methodologies".

Claim 1 and 15 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Kent et al., U.S. Patent No. 6,184,344.

Kent et al. disclose, see Figure 1 and discussion thereof and Examples 1-5 at cols. 11-16, a method for the fusion of proteins wherein the process of intramolecular acyl transfer is used to ligate a first target protein generated with a C-terminal thioester to a second target protein generated with a specified amino terminal amino acid, a cysteine, to form a fusion polypeptide. Claim 1 does not require **recombinant** expression of either a first or a second target protein, thus the design and preparation of the first and second target proteins of Kent et al. are considered to be expressions of proteins for purposes of this rejection, anticipating the claimed subject matter. In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method disclosed by Kent et al. with both a **recombinantly-expressed** first and second target protein because Kent et al. suggest, in the paragraph spanning cols. 8-9, that

proteins to be ligated by the method include those "expressed from by standard rec[ombinant]DNA means".

Claim 1 and 15 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Offord et al., U.S. Patent No. 6,168,784.

Available as prior art under 35 U.S.C. §102(e) in view of their provisional filing date, Offord et al. disclose, see cols. 6-8 and cols. 11-14, the preparation of a RANTES protein wherein the process of intramolecular acyl transfer is used to ligate a first target protein generated with a C-terminal thioester to a second target protein generated with a specified amino terminal amino acid, a cysteine, to form a fusion polypeptide. Claim 1 does not require **recombinant** expression of either a first or a second target protein, thus the design and preparation of the first and second target proteins of Offord et al. are considered to be expressions of proteins for purposes of this rejection, anticipating the claimed subject matter. In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method disclosed by Offord et al. with both a **recombinantly-expressed** first and second target protein because Offord et al. teach, col. 7, lines 56-58, that proteins ligated by the method include those made "ribosomally in a cell free system, or ribosomally within a cell".

Claim 1 and 15 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Hiatt et al., U.S. Patent No. 6,045,774.

Available as prior art under 35 U.S.C. §102(e) in view of their provisional filing date, Hiatt et al. disclose, see col. 18, lines 7-26, the preparation of a transmembrane protein wherein the process of intramolecular acyl transfer is used to ligate a first target protein generated with a C-terminal thioester to a second target protein generated with a specified amino terminal amino acid, a cysteine, to form a fusion polypeptide. Claim 1 does not require **recombinant** expression of either a first or a second target protein, thus the design and preparation of the first and second target proteins of Hiatt et al. are considered to be

expressions of proteins for purposes of this rejection, anticipating the claimed subject matter. In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the method disclosed by Hiatt et al. with both a recombinantly-expressed first and second target protein because Hiatt et al. teach, cols. 19-20, lines 56-58, that the transmembrane proteins may be produced recombinantly and because one of ordinary skill in the art at the time the invention was made would have appreciated that component proteins of a transmembrane protein may also be made recombinantly and ligated by the method and recognized the advantage of doing so where smaller component proteins would be more easily isolated from prokaryotic host cells than an integral transmembrane protein.

Claims 2, 7, 8, 9 and 14 are rejected under 35 U.S.C. §103(a) as being unpatentable over any of Canne et al., Tam, or Kent et al., as applied to claim 1 above, in view of Mills et al., 1998, **Proceedings of the National Academy of Sciences, USA**, Vol. 95, pages 3543-3548, of record.

The teachings of Canne et al., Tam, or Kent et al. are taken as before. While none of Canne et al., Tam, or Kent et al. teach the use of plasmid expression vectors and transformed host cells for recombinant expression of components of fusion polypeptides wherein the plasmid expression vectors comprise a nucleic acid sequence encoding a first target polypeptide fused at its carboxyl terminus to the amino terminus of an intein element, Mills et al. teach the use of a mutant intein in an *in vitro* method for trans-splicing, see pages 3543 and 3544 and Fig. 8, induced by adding dithiothreitol [DTT] and raising the temperature of the *in vitro* solution to 25°C, whereby splicing provides a new fusion protein from a first recombinantly expressed target protein and a second recombinantly expressed target protein, and wherein the first target protein comprised an amino-proximal target protein fused to a carboxyl-proximal mutant intein and the second target protein comprised an amino-proximal mutant intein fused to a carboxyl-proximal target protein. Mills et al. teach, page 3548, that their "results show that the N- and C-

terminal intein fragments essentially constitute a polypeptide ligase system that allows the *in vitro* ligation of any two proteins fused to such fragments".

It would have been obvious to one of ordinary skill in the art to substitute a recombinantly-expressed second target protein which is a fusion of an amino-proximal mutant intein and a carboxyl-proximal target protein according to Mills et al. and has an amino-terminal cysteine corresponding to a chemically-synthesized second target protein used by any of Canne et al., Tam, or Kent et al. in an *in vitro* method for fusion of first and second target proteins utilizing the first target protein of Mills et al. liberated by thiol reagent-induced cleavage from a fusion of an expressed amino-proximal target protein fused to a carboxyl-proximal intein and having a C-terminal thioester available for formation of a peptide bond with N-terminal cysteine of the second target protein. This is because Mills et al. teach that inteins present in separate fusion proteins should be excised *in vitro* to release target proteins for concurrent splicing *in vitro* to form a new fusion protein, and because Canne et al., Tam, and Kent et al. teach how such splicing may be conducted by providing a first target polypeptide having a C-terminal thioester to permit formation of a peptide bond with a nucleophilic attack upon the thioester by an amino-terminal cysteine of the second target protein, and because Mills et al. teach that mutant inteins may be used to promote the *in vitro* splicing of two recombinantly expressed target proteins encoded by separate nucleic acid sequences as fusion proteins each comprising a mutant intein borne by plasmid vectors.

Allowable Subject Matter

Claims 16-23, 25-27, 29 and 30 are allowed. Claims 3-6 and 10-13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The subject matters of methods of claims 3-6 and 10-13 are free of the prior art

of record which fails to suggest that one of ordinary skill in the art at the time the invention was made should use chitin affinity column purification or insert the *M. thermoautotrophicum* ribonucleoside-diphosphate reductase intein, see Figure 8 of Smith et al., made of record with Applicant's information disclosure statement, into any protein fusion partner in order to practice a method of claims 3-6 and 10-13.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. The examiner's direct FAX telephone number is 703.746.3169. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
April 19, 2002

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